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(54) Title: PROCESSES FOR THE PREPARATION OF ILOPERIDONE

(57) Abstract: The present invention provides processes for the preparation of 4'-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]propoxy]-3'-methoxyacetophenone.



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PROCESSES FOR THE PREPARATION OF ILOPERIDONE

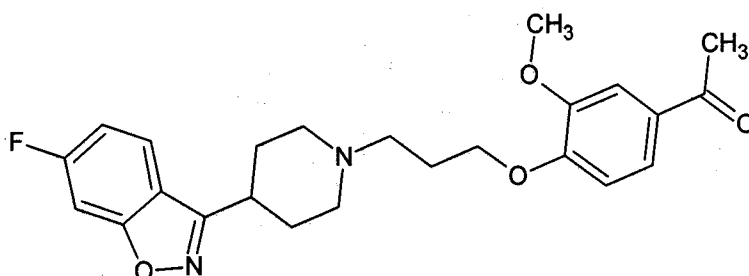
Field of the Invention

The present invention provides processes for the preparation of 4'-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]propoxy]-3'-methoxyacetophenone.

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Background of the Invention

4'-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino]propoxy]-3'-methoxyacetophenone (iloperidone), is a psychotropic agent known from U.S. RE 39,198 having the structure as represented by Formula I.



Formula I

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It is marketed in the United States under the brand name FANAPT® for the acute treatment of schizophrenia.

U.S. RE 39,198, WO 2004/006886 and WO 2010/031497 disclose processes for the preparation of iloperidone using ethanol or butyl acetate.

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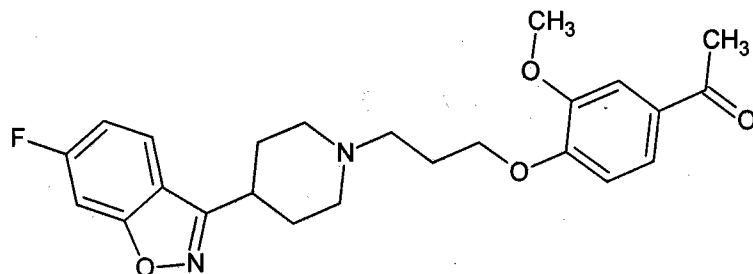
Besides ethanol and butyl acetate, no other solvent is disclosed in literature for the preparation of iloperidone.

Summary of the Invention

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The present invention provides processes for the preparation of iloperidone. The processes of the present invention are advantageous on an industrial scale as they provide highly pure iloperidone in a single step without the need for carrying out multiple crystallizations or any further purification.

A first aspect of the present invention provides processes for the preparation of pure iloperidone of Formula I

**Formula I**

comprising contacting crude iloperidone with solvent(s) selected from the group comprising of organic solvents containing at least one hydroxyl group, chlorinated hydrocarbons, ketones, alkyl acetates, amides, nitriles, ethers, sulphoxides and mixtures thereof, wherein the organic solvent is not absolute ethanol or butyl acetate.

A second aspect of the present invention provides iloperidone having purity greater than 99% as determined by HPLC.

Detailed Description of the Invention

Crude iloperidone may be obtained by any of the methods known in the literature such as those described in U.S. RE 39,198, WO 2004/006886 and WO 2010/031497, which are incorporated herein by reference. In general, crude iloperidone may be prepared by reacting 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole hydrochloride with 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone in the presence of potassium carbonate in dimethylformamide. Crude iloperidone, to be used as starting material for the preparation of pure iloperidone of the present invention, may be obtained as a solution in the reaction medium used for its preparation and used as such without isolation.

The meaning of the term “contacting”, as used herein, includes dissolving, slurring, stirring, or a combination thereof.

The starting crude iloperidone may be contacted with a solvent selected from the group consisting of mono- or polyhydric alcohols except absolute ethanol, hydrocarbons, chlorinated hydrocarbons, ketones, alkyl acetates except butyl acetate, amides, nitriles, ethers, sulphoxides, and mixtures thereof. Examples of mono- or polyhydric alcohols include methanol, 8% denatured spirit, n-propanol, isopropanol, n-butanol, sec-butanol, isobutanol, n-pentanol, glycerol or ethylene glycol. Examples of chlorinated hydrocarbons

include dichloromethane, chloroform, dichloroethane or carbon tetrachloride. Example of ketones includes acetone, methyl ethyl ketone or methyl isobutyl ketone. Examples of alkyl acetates include methyl acetate, ethyl acetate or propyl acetate. Examples of amides include N, N-dimethylformamide or N, N-dimethylacetamide. Examples of nitriles include acetonitrile or propionitrile. Examples of ethers include diethyl ether, ethyl methyl ether, tetrahydrofuran or 1, 4-dioxane. Examples of sulphoxides may include dimethyl sulfoxide or diethyl sulphoxide. The solvent is preferably selected from the group consisting of hydrocarbons, chlorinated hydrocarbons, ketones, amides, nitriles, ethers, sulphoxides, and mixtures thereof.

Crude iloperidone may be contacted with a solvent at a temperature of from about 15°C to the reflux temperature of the solvent. The reaction mixture may be stirred for a period of about 15 minutes to about 1 hour. Activated carbon may be added. The reaction mixture may be further stirred for a period of about 5 minutes to about 30 minutes and filtered. An anti-solvent may be added. The anti-solvent may be selected from the group comprising of hydrocarbons, such as hexane, cyclohexane, benzene, toluene, heptanes or octane. The reaction mixture may be again stirred for about 1 hour to about 5 hours.

Isolation may be accomplished by concentration, precipitation, cooling, filtration or centrifugation, or a combination thereof, followed by drying.

The processes of the present invention provide iloperidone having purity greater than 99% by HPLC. In one embodiment, the purity of iloperidone is greater than 99.5% by HPLC. In another embodiment, the purity of iloperidone is greater than 99.8% by HPLC.

In the foregoing section, embodiments are described by way of examples to illustrate the process of invention. However, these are not intended in any way to limit the scope of the present invention. Several variants of the examples would be evident to persons ordinarily skilled in the art which are within the scope of the present invention.

Methods

Chromatographic purity was determined by HPLC using a ZORBAX SB C-18, (250 x 4.6) mm, 5µm column with a flow rate: 1.0 mL/minute; column oven temperature:

40°C; Detector: 274 nm; Injection volume: 20L; Run time: 52 minutes using potassium dihydrogen orthophosphate in water as diluent and buffer.

Examples

Preparation of Crude Iloperidone

5 Example 1:

6-Fluoro-3-(4-piperidinyl)-1,2-benzisoxazole hydrochloride (25 g), 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone (23.65 g), potassium carbonate (26.88 g) and N, N-dimethylformamide (250 mL) were added to a reaction vessel at a temperature of about 20°C to 25°C. The temperature was slowly raised to about 90°C to 95°C in a period of about 1 hour. The reaction mixture was stirred for about 16 hours and then dispersed into de-ionized water (250 mL), extracted with ethyl acetate (2 x 125 mL) followed by washing with water (100 mL). Ethyl acetate was recovered under vacuum at a temperature of about 40°C to 45°C to obtain crude iloperidone.

Yield: 70%

15 HPLC Purity: 85-86%

Preparation of Pure Iloperidone

Example 2:

Dichloromethane (50 mL) was added to a reaction vessel containing crude iloperidone (10 g) at about 20°C to 25°C. The reaction mixture was stirred for about 30 minutes. Activated carbon (1 g) was added. The reaction mixture was stirred for about 15 minutes, filtered and washed with dichloromethane (10 mL). Hexane (10 mL) was added. The reaction mixture was stirred for about 2 hours, filtered, washed with hexane (10 mL) and dried under reduced pressure at about 40°C to 45°C for about 12 hours.

Yield: 47%

25 HPLC Purity: 99.63%

Example 3:

Chloroform (50 mL) was added to a reaction vessel containing crude iloperidone (10 g) at about 20°C to 25°C. The reaction mixture was stirred for about 30 minutes.

Activated carbon (1 g) was added. The reaction mixture was stirred for about 15 minutes, filtered and washed with dichloromethane (10 mL). Hexane (10 mL) was added. The reaction mixture was stirred for about 2 hours, filtered, washed with hexane (10 mL) and dried under reduced pressure at about 40°C to 45°C for about 12 hours.

5 Yield: 46%

HPLC Purity: 99.75%

Example 4:

Acetone (50 mL) was added to a reaction vessel containing crude iloperidone (10 g) at about 20°C to 25°C. The reaction mixture was refluxed for about 15 minutes.

10 Activated carbon (1 g) was added at the same temperature. The reaction mixture was stirred for about 15 minutes. The reaction mixture was filtered at the same temperature to remove activated carbon and washed with hot acetone (10 mL). The filtrate was heated to reflux to obtain a clear solution. The solution was cooled to a temperature of about 20°C to 25°C and stirred for about 2 hours. The reaction mixture was filtered, washed with
15 acetone (10 mL) and dried under reduced pressure at about 40°C to 45°C for about 12 hours.

Yield: 52%

HPLC Purity: 99.98%

Example 5:

20 Methyl iso-butyl ketone (50 mL) was added to a reaction vessel containing crude iloperidone (10 g) at about 20°C to 25°C. The reaction mixture was refluxed for about 15 minutes. Activated carbon (1 g) was added at the same temperature. The reaction mixture was stirred for about 15 minutes. The reaction mixture was filtered at the same temperature to remove activated carbon and washed with hot methyl iso-butyl ketone (10
25 mL). The filtrate was heated to reflux to obtain a clear solution. The solution was cooled to a temperature of about 20°C to 25°C and stirred for about 2 hours. The reaction mixture was filtered, washed with methyl iso-butyl ketone (10 mL) and dried under reduced pressure at about 40°C to 45°C for about 12 hours.

Yield: 47%

HPLC Purity: 99.84

Example 6:

Methanol (100 mL) was added to a reaction vessel containing crude iloperidone (10 g) at about 20°C to 25°C. The reaction mixture was refluxed for about 15 minutes.

- 5 Activated carbon (1 g) was added at the same temperature. The reaction mixture was stirred for about 15 minutes. The reaction mixture was filtered at the same temperature to remove activated carbon and washed with hot methanol (10 mL). The filtrate was heated to reflux to obtain a clear solution. The solution was cooled to a temperature of about 20°C to 25°C and stirred for about 2 hours. The reaction mixture was filtered, washed
- 10 with methanol (10 mL) and dried under reduced pressure at about 40°C to 45°C for about 12 hours.

Yield: 55%

HPLC Purity: 99.67%

Example 7:

- 15 8% Denatured spirit (100 mL) was added to a reaction vessel containing crude iloperidone (10 g) at about 20°C to 25°C. The reaction mixture was refluxed for about 15 minutes. Activated carbon (1 g) was added at the same temperature. The reaction mixture was stirred for about 15 minutes. The reaction mixture was filtered at the same
- 20 temperature to remove activated carbon and washed with hot denatured spirit (8%, 10 mL). The filtrate was heated to reflux to obtain a clear solution. The solution was cooled to a temperature of about 20°C to 25°C and stirred for about 2 hours. The reaction mixture was filtered, washed with denatured spirit (8%, 10 mL) and dried under reduced pressure at about 40°C to 45°C for about 12 hours.

Yield: 56%

- 25 HPLC Purity: 99.39%

Example 8:

Ethyl acetate (50 mL) was added to a reaction vessel containing crude iloperidone (10 g) at about 20°C to 25°C. The reaction mixture was refluxed for about 15 minutes.

Activated carbon (1 g) was added at the same temperature. The reaction mixture was

stirred for about 15 minutes. The reaction mixture was filtered at the same temperature to remove activated carbon and washed with hot ethyl acetate (10 mL). The filtrate was heated to reflux to obtain a clear solution. The solution was cooled to a temperature of about 20°C to 25°C and stirred for about 2 hours. The reaction mixture was filtered, washed with ethyl acetate (10 mL) and dried under reduced pressure at about 40°C to 45°C for about 12 hours.

Yield: 43%

HPLC Purity: 99.74%

Example 9:

Iso-propanol (50 mL) was added to a reaction vessel containing crude iloperidone (10 g) at about 20°C to 25°C. The reaction mixture was refluxed for about 15 minutes. Activated carbon (1 g) was added at the same temperature. The reaction mixture was stirred for about 15 minutes. The reaction mixture was filtered at the same temperature to remove activated carbon and washed with hot iso-propanol (10 mL). The filtrate was heated to reflux to obtain a clear solution. The solution was cooled to a temperature of about 20°C to 25°C and stirred for about 2 hours. The reaction mixture was filtered, washed with iso-propanol (10 mL) and dried under reduced pressure at about 40°C to 45°C for about 12 hours.

Yield: 57%

HPLC Purity: 99.41%

Example 10:

N, N-dimethylformamide (50 mL) was added to a reaction vessel containing crude iloperidone (10 g) at about 20°C to 25°C. The reaction mixture was refluxed for about 15 minutes. Activated carbon (1 g) was added at the same temperature. The reaction mixture was stirred for about 15 minutes. The reaction mixture was filtered at the same temperature to remove activated carbon and washed with hot N, N-dimethylformamide (10 mL). The filtrate was heated to reflux to obtain a clear solution. The solution was cooled to a temperature of about 20°C to 25°C and stirred for about 2 hours. The reaction mixture was filtered, washed with N, N-dimethylformamide (10 mL) and dried under reduced pressure at about 40°C to 45°C for about 12 hours.

Yield: 40%

HPLC Purity: 99.79%

Example 11:

Acetonitrile (50 mL) was added to a reaction vessel containing crude iloperidone (10 g) at about 20°C to 25°C. The reaction mixture was refluxed for about 15 minutes. Activated carbon (1 g) was added at the same temperature. The reaction mixture was stirred for about 15 minutes. The reaction mixture was filtered at the same temperature to remove activated carbon and washed with hot acetonitrile (10 mL). The filtrate was heated to reflux to obtain a clear solution. The solution was cooled to a temperature of about 20°C to 25°C and stirred for about 2 hours. The reaction mixture was filtered, washed with acetonitrile (10 mL) and dried under reduced pressure at about 40°C to 45°C for about 12 hours.

Yield: 51%

HPLC Purity: 99.86%

15 Example 12:

Methanol:Acetone :: 1:1 mixture (50 mL) was added to a reaction vessel containing crude iloperidone (10 g) at about 20°C to 25°C. The reaction mixture was refluxed for about 15 minutes. Activated carbon (1 g) was added at the same temperature. The reaction mixture was stirred for about 15 minutes. The reaction mixture was filtered at the same temperature to remove activated carbon and washed with hot methanol:acetone :: 1:1 mixture (10 mL). The filtrate was heated to reflux to obtain a clear solution. The solution was cooled to a temperature of about 20°C to 25°C and stirred for about 2 hours. The reaction mixture was filtered, washed with methanol:acetone :: 1:1 mixture (10 mL) and dried under reduced pressure at about 40°C to 45°C for about 12 hours.

Yield: 41%

HPLC Purity: 99.83%

Example 13:

Acetone:iso-propanol :: 1:1 mixture (50 mL) was added to a reaction vessel containing crude iloperidone (10 g) at about 20°C to 25°C. The reaction mixture was refluxed for about 15 minutes. Activated carbon (1 g) was added at the same temperature.

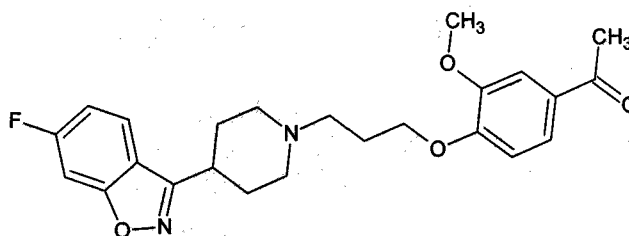
- 5 The reaction mixture was stirred for about 15 minutes. The reaction mixture was filtered at the same temperature to remove activated carbon and washed with hot acetone:iso-propanol :: 1:1 mixture (10 mL). The filtrate was heated to reflux to obtain a clear solution. The solution was cooled to a temperature of about 20°C to 25°C and stirred for about 2 hours. The reaction mixture was-- filtered, washed with acetone:iso-propanol ::
- 10 1:1 mixture (10 mL) and dried under reduced pressure at about 40°C to 45°C for about 12 hours.

Yield: 51%

HPLC Purity: 99.75%

We Claim:

- 1 1. A process for the preparation of pure iloperidone of Formula I



2 **Formula I**

- 3 comprising contacting crude iloperidone with a solvent selected from the group consisting
4 of mono- or poly-hydric alcohols, chlorinated hydrocarbons, ketones, alkyl acetates,
5 amides, nitriles, ethers, sulfoxides and mixtures thereof, with the proviso that the solvent
6 is not absolute alcohol or butyl acetate.

- 1 2. The process according to claim 1, wherein crude iloperidone is contacted with
2 solvent at a temperature of about 15°C to the reflux temperature of the solvent.

- 1 3. The process according to claim 1, wherein an anti-solvent is added to the reaction
2 mixture.

- 1 4. The process according to claim 3, wherein the anti-solvent is selected from
2 hydrocarbon such as hexane, cyclohexane, benzene, toluene, heptanes or octane.

- 1 5. The process according to claim 1, wherein the solvent used is methanol, 8%
2 denatured spirit or iso-propanol.

- 1 6. The process according to claim 1, wherein the solvent used is chloroform or
2 dichloromethane.

- 1 7. The process according to claim 1, wherein the solvent used is acetone or methyl
2 iso-butyl ketone.

- 1 8. The process according to claim 1, wherein the solvent used is ethyl acetate.

- 1 9. The process according to claim 1, wherein the solvent used is N, N-
2 dimethylformamide.

- 1 10. The process according to claim 1, wherein the solvent used is acetonitrile.

- 1 11. The process according to claim 1, wherein a mixture of alcohol and ketone is used
2 as solvent.
- 1 12. The process according to claim 1, wherein a mixture of methanol and acetone is
2 used as solvent.
- 1 13. The process according to claim 1, wherein a mixture of iso-propanol and acetone is
2 used as solvent.
- 1 14. The process according to claim 1, wherein a 1:1 mixture of solvents is used.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2011/055919

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/04 B01D9/02
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D B01D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	example 3	1,2,5,6
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Y	example 1	1,2,5,6
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Y	page 6, line 6 - line 7	1,2,5,6
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☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2011/055919

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2011/055919

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